Prior Antimicrobial Agent Use Increases the Risk of Sporadic Infections with Multidrug-Resistant *Salmonella enterica* Serotype Typhimurium: A FoodNet Case-Control Study, 1996–1997

M. Kathleen Glynn,[1] Vasudha Reddy,[1] Lori Hutwagner,[1] Therese Rabatsky-Ehr,[3] Beletshachew Shiferaw,[4] Duc J. Vugia,[5] Suzanne Segler,[2] Jeff Bender,[6] Timothy J. Barrett,[1] Frederick J. Angulo,[1] and the Emerging Infections Program FoodNet Working Group[a]

[1]Division of Bacterial and Mycotic Disease, National Center for Infectious Disease, Centers for Disease Control and Prevention, and [2]Emerging Infections Program, Atlanta, Georgia; [3]Emerging Infections Program, New Haven, Connecticut; [4]Oregon Department of Human Services, Office of Disease Prevention and Epidemiology, Portland; [5]California Department of Health Services, Berkeley; and [6]Minnesota Department of Health, Minneapolis

Several strains of multidrug-resistant (MDR) *Salmonella* serotype Typhimurium, including MDR *S.* Typhimurium definitive type 104, cause almost 10% of *Salmonella* infections among humans in the United States. To determine the risk factors for acquiring sporadic MDR *S.* Typhimurium infection, we conducted a population-based, case-control study using data from the Foodborne Diseases Active Surveillance Network (FoodNet) during 1996–1997. *S.* Typhimurium isolates from 5 FoodNet surveillance areas (California, Connecticut, Georgia, Minnesota, and Oregon) were tested for antimicrobial resistance and phage typing. Telephone interviews were conducted with ill persons and matched control subjects. Compared with both control subjects and patients infected with pansensitive strains of *S.* Typhimurium, patients with MDR *S.* Typhimurium infection were significantly more likely to have received an antimicrobial agent, particularly an agent to which the *Salmonella* isolate was resistant, during the 4 weeks preceding illness onset. Prudent antimicrobial agent use among humans and among veterinarians and food-animal producers is necessary to reduce the burden of drug-resistant salmonellosis in humans.

Each year in the United States, an estimated 1.4 million *Salmonella* infections occur [1]. Most infections are mild or moderate, but severe infections can occur, including bacteremia and meningitis; *Salmonella* infections result in an estimated 580 deaths annually. The estimated costs of medical care and loss of productivity resulting from foodborne salmonellosis are $0.5–$2.3 billion/year [2]. Among the >2000 serotypes of *Salmonella enterica,* serotype Typhimurium (including variant Copenhagen) is the most common; it accounted for 25% of culture-confirmed infections reported to the Centers for Disease Control and Prevention (CDC) in 1999 [3]. Increasing antimicrobial resistance among *Salmonella* has been noted for several decades [4–6]; compared with other serotypes, increasing antimicrobial resistance (including resistance to multiple agents) is particularly common among strains of serotype Typhimurium [7]. During the past decade, 1 multidrug-resistant (MDR; defined as resistant to ⩾5 antimicrobial agents) strain of *S.* Typhimurium in particular

Financial support: Centers for Disease Control and Prevention, National Center for Infectious Diseases; US Department of Agriculture, Food Safety and Inspection Service; and US Food and Drug Administration, Center for Food Safety and Applied Nutrition.

[a] Working group members are listed at the end of the text.

Reprints: Dr. Frederick J. Angulo, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, MS A-38, Atlanta, GA 30333 (fangulo@cdc.gov). Correspondence: Dr. M. Kathleen Glynn, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, MS E-47, Atlanta, GA 30333 (kglynn@cdc.gov).

Clinical Infectious Diseases 2004;38(Suppl 3):S227–36

1058-4838/2004/3808S3-0016

has emerged in the United States and internationally. This strain, MDR *S.* Typhimurium definitive type (DT) 104, is usually resistant to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline (ACSSuT) [6, 8]. In 1999, MDR *S.* Typhimurium resistance (R) type ACSSuT accounted for 6.8% of *Salmonella* isolates in the National Antimicrobial Resistance Monitoring System (NARMS) in the United States [7]. Recently, a second MDR strain of *S.* Typhimurium that is resistant to at least ampicillin, kanamycin, streptomycin, sulfamethoxazole, and tetracycline (designated R type AKSSuT) has also been described, and it accounted for an additional 2.6% of NARMS *Salmonella* isolates in 1999 [7]. A third strain that had a combination of the 2 resistance patterns (R type ACKSSuT) was less common but accounted for an additional 0.8% of NARMS *Salmonella* isolates in 1999.

Studies in the United States have consistently identified contaminated food to be the source for most nontyphoidal *Salmonella* infections among humans and, by extension, also for infections with antimicrobial-resistant *Salmonella* [9–11]. In the United States, most human *Salmonella* infections are acquired from eating food contaminated with animal feces; such foods are commonly of animal origin but also include other foods (e.g., produce) that can be contaminated through irrigation with contaminated surface water. Infections resulting from direct contact with animals are less common, but they do occur. Person-to-person transmission of *Salmonella* in the United States is uncommon, primarily because of improvements in sanitary practices that limit the dissemination of human feces [9].

Although MDR *S.* Typhimurium, particularly R types ACSSuT and AKSSuT, has become prevalent in the United States, few studies have been conducted to determine the risk factors for infection among humans. Studies that have been conducted specifically to address the role of MDR strains of *S.* Typhimurium in outbreaks have associated these infections with the consumption of animal products (e.g., pork in Denmark [12] and unpasteurized cheese in the United States [13, 14]). No study has examined the risk factors for acquiring sporadic MDR *S.* Typhimurium infection in this country. Our goal, therefore, was to identify the risks for acquiring sporadic MDR *S.* Typhimurium infection and to assess the clinical differences between persons infected with MDR *S.* Typhimurium and those infected with pansensitive *S.* Typhimurium.

METHODS

Surveillance. The Foodborne Diseases Active Surveillance Network (FoodNet), in collaboration with participating state health departments, conducted active surveillance at clinical laboratories during 1996–1997 for culture-confirmed cases of *S.* Typhimurium infection in 5 areas (the states of Minnesota and Oregon and selected counties in California, Connecticut, and Georgia) with a combined population of 14,281,096 persons [15]. FoodNet personnel contacted each of the clinical laboratories that processed clinical samples from residents of FoodNet surveillance areas (also known as "FoodNet sites") at least monthly to ascertain culture-confirmed cases. Identified *Salmonella* isolates were then routinely forwarded from clinical laboratories to their respective state public health laboratories for serotyping.

Laboratory methods. *S.* Typhimurium isolates, after being serotyped at the state public health laboratories in the FoodNet sites, were tested at the Foodborne and Diarrheal Diseases Laboratory at the CDC for antimicrobial susceptibility. Partial-range MICs were determined for 14 antimicrobial agents: amikacin, amoxicillin/clavulanic acid, ampicillin, ceftriaxone, cephalothin, chloramphenicol, ciprofloxacin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim-sulfamethoxazole, using broth microdilution (Sensititer; Trek Diagnostics). NCCLS interpretive standards were used [16]. Isolates that were resistant to $\geqslant$5 antimicrobial agents were categorized as being MDR. Groups of isolates with similar R types were not mutually exclusive; isolates with R types ACKSSuT were counted among the R type ACSSuT and AKSSuT groups. After undergoing resistance testing, isolates were phage typed using methods described elsewhere [17]. Isolates phage typed as DT104, DT104a, DT104b, DT104c, or U302 were classified together as DT104 complex (referred to hereafter as "DT104 isolates"). Isolates identified as phage types other than DT104 and those typed as reacting to phages but not conforming to a specific phage type, rough, or untypeable were classified as "other *S.* Typhimurium."

Case-control study. With the exception of residents of Minnesota, all persons living in the surveillance area who were identified as having culture-confirmed *S.* Typhimurium infection during the study period were eligible for inclusion in the study. In Minnesota, a 2-stage selection procedure was used. First, every third serogroup B and D *Salmonella* isolate was randomly selected; then, of the selected isolates, all serotype Typhimurium isolates were identified; all corresponding patients from whom these isolates had been obtained were eligible for inclusion in the case-control study. Telephone interviews using a fixed questionnaire were conducted by state FoodNet staff members. Persons with culture-confirmed *S.* Typhimurium infection were surveyed, along with 1 or 2 healthy control subjects who were matched to case patients by age and telephone exchange; control subjects were selected by sequential-progressive-digit dialing. For infants aged <2 years, control subjects were also found through matching to birth registries. Information was collected concerning illness, treatment, and outcome for all persons with a *S.* Typhimurium infection; in addition, interviewees were asked about ~100 potential food,

Table 1. Resistance to antimicrobial agents among 489 *Salmonella* Typhimurium isolates that underwent susceptibility testing, FoodNet case-control study, 1996–1997.

Antimicrobial agent	NCCLS breakpoint MIC, μg/mL	No. (%) of resistant isolates
Amikacin	⩾64	0 (0)
Amoxicillin/clavulanic acid	⩾32/⩾16	16 (3)
Ampicillin	⩾32	205 (42)
Ceftriaxone	⩾64	2 (<1)
Cephalothin	⩾32	18 (4)
Chloramphenicol	⩾32	142 (29)
Ciprofloxacin	⩾4	0 (0)
Gentamicin	⩾16	14 (3)
Kanamycin	⩾64	63 (13)
Nalidixic acid	⩾32	5 (1)
Streptomycin	⩾64	228 (47)
Sulfamethoxazole	⩾512	272 (56)
Tetracycline	⩾16	213 (44)
Trimethoprim-sulfamethoxazole	⩾4/⩾76	10 (2)

water, and other exposures (e.g., international travel and visiting a farm). Patients were interviewed within 21 days after specimens were obtained from them; control subjects were interviewed within 10 days (7 days in Connecticut) of the interview of their matched patient.

Patients were excluded from the study if they did not have diarrhea, if the onset of diarrhea due to the culture-confirmed *S.* Typhimurium infection occurred ⩾10 days before the date the specimen was obtained, if the patient was not the first infected person in the household, or if the patient's infection belonged to a known outbreak. Only patients for whom isolates were both phage typed and tested for antimicrobial susceptibility were included in the analysis. We obtained informed consent from participants and conducted the study in accordance with guidelines for human research as specified by the US Department of Health and Human Services.

Statistical analysis. Three main comparisons were performed: (1) between persons infected with *S.* Typhimurium (regardless of susceptibility results) and matched healthy control subjects, (2) between the subset of persons infected with MDR *S.* Typhimurium and matched healthy control subjects, and (3) between persons infected with MDR *S.* Typhimurium and those infected with pansensitive *S.* Typhimurium. All analyses were conducted using SAS version 6.12 software (SAS Institute). Between-group comparisons were conducted using the *t*-test statistic for means and the χ^2 statistic for proportions; $P < .05$ was considered to be significant. We used conditional logistic regression for analyses between matched case patients and control subjects and unconditional logistic regression for the final unmatched comparison. Multivariate analysis included variables that were associated with the outcome of interest according to the results of univariate analysis ($P < .10$). In the unconditional logistic regression model, age group (i.e., <2, 2–12, 13–18, 19–60, and >60 years), FoodNet site, and season of the year (i.e., January–March, April–June, July–September, and October–December) were included in the multivariate model. We conducted forward stepwise regression modeling in the multivariate analysis to identify risk factors that were independently associated with the outcome of interest ($P < .05$). Because we wanted to identify the exposures associated with infection, risk factors negatively associated with the outcome were not included in further models unless they were thought to be confounders. The population-attributable fraction was calculated for each of the variables that were independently associated with the outcome according to the final model [18]. CIs were computed for model-adjusted, exposure-specific attributable fractions with use of a jackknife procedure [19].

RESULTS

During the 12-month study period, 647 culture-confirmed cases of *S.* Typhimurium infection were ascertained from the 5 FoodNet sites. The overall incidence was 4.3 cases/100,000 population, and ranged from 3.3 in Oregon to 4.7 in Connecticut and California. Fifty percent of patients were female, and the median age was 13 years (25%–75% quartiles, 3–36 years). Among patients with known outcome information, 157 (25%) of 622 were hospitalized, and 5 (0.8%) of 619 died.

From the 647 patients with culture-confirmed *S.* Typhimurium infection, 503 (78%) isolates were available for further laboratory testing. Of these, 489 (97%) underwent antimicrobial susceptibility testing. Isolates were most frequently resistant to sulfamethoxazole (56% of isolates), streptomycin (47%), tetracycline (44%), and ampicillin (42%); no isolate was resistant to amikacin or ciprofloxacin (table 1). Of the 489 isolates, 197 (40%) were pansensitive, 144 (29%) were resistant to 5 agents, and the remaining isolates exhibited resistance to a varying number of agents; the most resistant isolate was resistant to 10 different agents (figure 1). Of the 179 MDR isolates, 135 (75%) were R type ACSSuT, 46 (26%) were R type AKSSuT, and 8 (4%) were R type ACKSSuT (table 2). Some of the 135 R type ACSSuT isolates were additionally resistant to nalidixic acid (2 isolates), amoxicillin/clavulanic acid (12), cephalothin (1), gentamicin (1), and trimethoprim-sulfamethoxazole (1). Some of the 46 R-type AKSSuT isolates were additionally resistant to cephalothin (10 isolates), nalidixic acid (1), gentamicin (1), and amoxicillin/clavulanic acid (1). Some of the 8 R type ACKSSuT isolates were additionally resistant to amoxicillin/clavulanic acid (2), ceftriaxone (1), cephalothin (1), and nalidixic acid (1). Only 6 (3%) MDR isolates were R types other than ACSSuT, AKSSuT, or ACKSSuT.

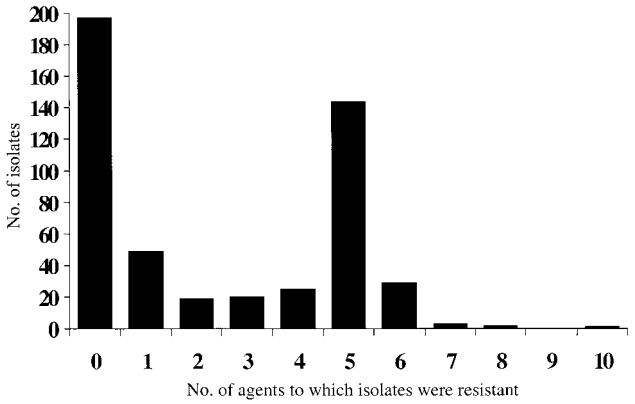

Figure 1. Occurrence of resistance among 489 *Salmonella* Typhimurium isolates tested for susceptibility to 14 antimicrobial agents, FoodNet case-control study, 1996–1997.

Of the 489 *S.* Typhimurium isolates with antimicrobial susceptibility test results, 488 (99%) underwent phage typing. Of these, 156 (32%) were phage typed as DT104 complex, and 332 isolates (68%) were other phage types or had other phage-typing results (table 2). Of the 179 MDR isolates, 123 (69%) were phage typed as DT104 complex; among 309 isolates that were pansensitive or resistant to <5 agents, only 33 (11%) were DT104 complex. Among the MDR isolates, 119 (88%) of 135 R type ACSSuT isolates were phage typed as DT104 complex, whereas only 6 (13%) of 46 R type AKSSuT isolates were phage typed as DT104 complex.

The proportion of the 488 fully characterized *S.* Typhimurium isolates that were MDR varied significantly across the 5 FoodNet sites ($P = .02$). California had the highest percentage of MDR isolates (50%), and Minnesota had the lowest (29%). Compared with other sites, Minnesota had a significantly higher proportion of MDR isolates that were R type AKSSuT (37% vs. 21%; $P = .03$). No demographic or other described attributes could clearly account for these differences between states.

Of the 488 patients whose isolates underwent both phage typing and antimicrobial susceptibility testing, 202 (41%) eligible patients were interviewed. Of the remaining 286 patients, 72 (25%) were excluded from the study because they were not interviewed within 21 days after a specimen was obtained; 64 (22%) were excluded because they were not eligible, most commonly because they were not randomly sampled for interview (37 patients), had onset of diarrhea >10 days before a specimen was obtained (12), or did not have diarrhea (9); 13 (5%) were excluded because they refused or were unable to answer interview questions; and 137 (48%) were lost to follow up or otherwise lacked a documented reason for exclusion. Of the 202 interviewed patients, 166 (82%) were matched to healthy control subjects and were included in the case-control study; 151 patients were matched with 2 control subjects, and 15 were matched with 1 control subject, for a total of 317 healthy control subjects. The remaining 36 interviewed patients (18%) were excluded after interview because healthy control subjects were not identified within the required time period.

By definition, all 202 interviewed patients reported diarrhea as a symptom. Of those providing information on additional symptoms, 109 (55%) of 197 reported a maximum of >10 loose stools over a 24-h period. Patients reported diarrhea lasting for a median of 7 days (range, 1–76 days); only 3 patients (1%) reported diarrhea that lasted >30 days. Other symptoms reported by patients included fever (88% of patients; median maximum temperature, 39°C; range, 38°C–41°C), abdominal cramps (91%), bloody diarrhea (65%), and vomiting (51%). For 155 (91%) of 171 responding patients, the illness interfered with normal activities; the median duration of interference was of 7 days (range, 0–76 days). Twenty-four percent of patients were hospitalized for this illness; the median duration of hospitalization was 3 days (range, 1–24 days). Of 198 responding patients, 116 (59%) patients who were treated with an antibiotic for their illness. Of these 116, 89 (77%) reported the particular agents they were treated with; of these, 7 (8%) were treated with an antimicrobial agent to which their isolate was resistant. Of the 202 isolates, 197 (98%) were cultured from stool; only 5 isolates (2%) were cultured from blood.

Of the 202 interviewed patients, 77 (38%) were infected with MDR isolates, 37 (18%) were infected with isolates resistant to 1–4 antimicrobial agents, and 88 (44%) were infected with pansensitive isolates. Of the 77 MDR isolates, 58 (75%) were R type ACSSuT and 21 (27%) were R type AKSSuT; 51 (66%) were DT104 R type ACSSuT. Controlling for age, season, and FoodNet site, we compared the spectrum of clinical illness between persons infected with MDR isolates and those infected with pansensitive isolates by examining the percentage of patients hospitalized or treated with antimicrobial agents for the *S.* Typhimurium infection, the percentage of isolates cultured from blood, and the frequency of different signs and symptoms between the 2 groups. No significant difference between the 2 patient groups was identified for any of the characteristics. The subset of patients with R type ACSSuT infections were slightly less likely to have missed usual activities than were patients infected with pansensitive strains (85% vs. 94%; $P = .03$). No significant differences were observed when the spectrum of clinical illness was compared between patients with R type AKSSuT infections and those infected with pansensitive strains.

With a few exceptions, the demographic characteristics of the patients and the microbiological characteristics of corresponding isolates (susceptibility testing and phage typing) were similar for the group of 202 interviewed patients and the group of 286 patients who were not interviewed. Patients who were not interviewed were more likely to have had their isolate cultured from extraintestinal sources than patients who were interviewed (9% vs. 3%; $P = .002$). Patients who were not in-

Table 2. Antimicrobial resistance and phage typing results for 488 *Salmonella* Typhimurium isolates, FoodNet case-control study, 1996–1997.

	No. (%) of isolates, by resistance class and type							
	Multidrug resistant[a]					Not multidrug resistant		
Strain	ACSSuT[b]	AKSSuT[b]	ACKSSuT[b]	Other patterns	Total[c]	Resistant to 1–4 agents	Pansensitive	Total[c]
DT104 complex								
DT104	81	5	5	3	84	12	2	98
DT104a	2	0	0	0	2	5	4	11
DT104b	30	0	0	0	30	0	2	32
U302	6	1	0	0	7	1	7	15
Subtotal	119	6	5	3	123	18	15	156 (32)
Other[d]								
RDNC	5	10	0	1	16	53	123	192
Untypeable	2	26	1	2	29	19	18	66
Rough	1	3	1	0	3	2	6	11
DT10	0	0	0	0	0	6	9	15
DT120	8	1	1	0	8	1	3	12
Other phage types	0	0	0	0	0	120	22	36
Subtotal	16	40	3	3	56	95	181	332 (68)
Total	135	46	8	6	179 (37)	113 (23)	196 (40)	488

NOTE. ACSSuT, resistant to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline; AKSSut, resistant to at least ampicillin, kanamycin, streptomycin, sulfamethoxazole, and tetracycline; DT, definitive type; RDNC, reacts to phages but does not conform to a specific phage type.

[a] Multidrug resistant isoaltes were defined as those resistant to ⩾5 antimicrobial agents.

[b] Groups of isolates with similar resistance types are not mutually exclusive: ACKSSuT isolates are included in ACSSuT, AKSSuT, and ACKSSuT columns.

[c] Row totals do not equal the sum of column values because groups of isolates with similar resistance types are not mutually exclusive.

[d] Other phage types or phage-typing results

terviewed were, on average, older (median age, 27 years; range, 1–94 years) than patients interviewed for the study (median age, 18 years; range, 1–83 years; $P = .001$). Additional identified differences were observed when the 166 patients who had at least 1 matched healthy control subject were compared with the 36 patients for whom control subjects could not be found. The 166 interviewed patients who were included in the case-control study were significantly older (median age, 20 years; range, 0–83 years) than the 36 patients without matched healthy control subjects (median age, 7 years; range, 0–46 years; $P = .001$). In addition, when compared with patients without matched healthy control subjects, patients included in the case-control study were more likely to be white (78% vs. 49%), less likely to be of a race other than those specified in the provided categories (5% vs. 19%), and less likely to be Hispanic (11% vs. 32%).

To identify the risk factors for infection with *S.* Typhimurium, we compared the 166 interviewed patients with the 317 matched healthy control subjects. In univariate analysis, several exposures occurring in the 5 days preceding illness onset were identified as risk factors for developing a *S.* Typhimurium infection—eating eggs (specifically scrambled or fried eggs) prepared outside the home (e.g., in a restaurant, deli, or cafeteria), visiting a cattle farm, traveling outside the United States, and eating <10 meals prepared in the home (table 3). Treatment with any antibiotic during the 4 weeks preceding illness onset was more common among case patients (17%) than among control subjects (10%). Treatment with an agent included in the common multidrug resistance patterns (i.e., R types ACSSuT, AKSSuT, and ACKSSuT) had a stronger association: 10% of case patients received ⩾1 of these agents during the 4 weeks preceding illness onset, compared with 4% of control subjects during the same time period (matched OR [MOR], 2.8; 95% CI, 1.3–6.1). Antimicrobial agents from the ACKSSuT group that were used to treat patients during the 4 weeks preceding illness onset included amoxicillin (in 13 patients) and penicillin (in 4). Agents from the ACKSSuT group that were used to treat healthy control subjects during the same 4-week time period as the matched case patients were amoxicillin (in 11 patients) and sulfamethoxazole (in 1). In the multivariate model, 3 exposures remained independently associated with the development of *S.* Typhimurium infection: receiving 1 of the agents in the ACKSSuT group during the 4 weeks preceding illness onset (MOR, 3.1; 95% CI, 1.3–7.3), traveling outside the

Table 3. Risk factors for *Salmonella* Typhimurium infection, FoodNet case-control study, 1996–1997.

	All infected patients vs. matched healthy control subjects			Patients infected with MDR strains vs. matched healthy control subjects			Patients infected with MDR strains vs. patients infected with pansensitive strains		
Risk factor	No. (%) of patients (n = 166)	No. (%) of control subjects (n = 317)	MOR (95% CI)	No. (%) of patients (n = 61)	No. (%) of control subjects (n = 117)	MOR (95% CI)	No. (%) of patients with MDR strains (n = 77)	No. (%) of patients with pansensitive strains (n = 88)	OR (95% CI)
In the 4 weeks before illness[a]									
Received agent(s) in the ACKSSuT group	17 (10)	12 (4)	2.86 (1.3–6.1)[b,c]	13 (22)	5 (5)	5.7 (1.8–17.4)[b,c]	15 (21)	2 (2)	19.7 (3.7–105.7)[b,c]
In the 5 days before illness onset[a]									
Ate eggs prepared outside the home	27 (18)	30 (10)	1.9 (1.0–3.3)[b]	12 (22)	13 (12)	2.2 (0.9–5.6)[b]	12 (21)	11 (15)	2.4 (0.8–7.0)
Ate <10 meals prepared in the home	94 (63)	158 (54)	1.6 (1.1–2.6)[b]	38 (71)	57 (54)	2.5 (1.2–5.2)[b]	41 (71)	44 (61)	1.7 (0.7–4.1)
Ate turkey prepared in the home	17 (10)	37 (13)	0.8 (0.4–1.5)	11 (19)	12 (11)	2.0 (0.8–5.0)	11 (17)	5 (6)	3.3 (0.9–11.4)[b,c]
Ate fried eggs prepared outside the home	12 (8)	8 (3)	2.8 (1.1–6.9)[b,c]	5 (9)	4 (4)	2.3 (0.6–8.7)	5 (8)	5 (7)	2.4 (0.5–10.8)
Ate scrambled eggs prepared outside the home	15 (10)	16 (6)	1.9 (0.9–4.2)[b]	8 (15)	7 (6)	3.2 (0.9–10.8)[b,c]	8 (14)	5 (7)	2.5 (0.7–9.7)
Visited a cattle farm	10 (6)	9 (3)	3.1 (1.0–9.4)[b]	3 (5)	3 (3)	2.4 (0.4–15.0)	3 (4)	5 (6)	1.3 (0.3–6.8)
Traveled outside the United States	8 (5)	2 (1)	13.6 (1.7–110.1)[b,c]	2 (3)	0 (0)	…	2 (3)	5 (6)	1.5 (0.2–10.7)

NOTE. ACKSSuT, ampicillin, chloramphenicol, kanamycin, streptomycin, sulfamethoxazole, and tetracycline; MDR, resistant to ⩾5 antimicrobial agents; MOR, matched odds ratio.

[a] Or similar period for control subjects.
[b] Significant according to univariate analysis ($P \leqslant .10$).
[c] Remained significant according to multivariate analysis ($P < .05$).

United States (MOR, 19.4; 95% CI, 2.2–172.4) during the 5 days preceding illness onset, and eating fried eggs prepared outside the home (MOR, 4.2; 95% CI, 1.4–12.9) during the 5 days before illness onset.

Of the 166 interviewed and matched patients, 61 (37%) were infected with MDR isolates. Forty-eight of the isolates (79%) were R type ACSSuT, 14 (23%) were R type AKSSuT, and 43 (70%) were DT104 R type ACSSuT. To determine the risk factors specifically for MDR *S.* Typhimurium infection, we compared the 61 patients who were infected with MDR isolates with their 117 matched healthy control subjects. In the univariate analysis, many of the same risk factors were identified as in the first analysis (table 3). Again, case patients were more likely to have eaten <10 home-cooked meals in the 5 days preceding illness onset and were more likely to have been treated with agents in the ACKSSuT group during the 4 weeks before illness onset (amoxicillin [in 12 patients] or penicillin [in 1]) than were control subjects during the same time period. In multivariate analysis, 2 variables remained in the final model: receiving agents in the ACKSSuT group during the 4 weeks before illness onset (MOR, 5.8; 95% CI, 1.6–20.7) and consuming scrambled eggs prepared outside the home during the 5 days before illness onset (MOR, 5.7; 95% CI, 1.3–26.1). As expected, a significant correlation was observed between this latter risk factor and having eaten <10 meals in the home during the same time period. Similar results were found when the analysis was restricted to the 43 patients with infected with MDR *S.* Typhimurium DT104 (R type ACSSuT) strains and their 84 matched healthy control subjects; these patients were more likely to have been treated with agents in the ACKSSuT group during the 4 weeks before illness (MOR, 5.5; 95% CI, 1.3–23.8) and to have consumed eggs outside the home during the 5 days before illness onset (MOR, 4.4; 95% CI, 1.2–16.6) than were matched control subjects in the same time periods.

We compared the 105 patients who had other *S.* Typhimurium infections (i.e., those infected with isolates resistant to <5 agents or that were pansensitive) with 200 matched healthy control subjects and found that eating fried eggs prepared outside the home, visiting a cattle farm, and traveling outside the United States during the 5 days before illness onset were again significantly associated with having an *S.* Typhimurium infection, according to the results of univariate analysis. In contrast, neither treatment with any antimicrobial agents nor treatment specifically with agents in the ACKSSuT group during the 4 weeks before illness onset was associated with infection with a strain of *S.* Typhimurium that was not MDR. Similarly, when we compared only the 76 patients who were infected with pansensitive strains with 142 matched healthy control subjects, neither prior use of any antimicrobial agent nor the use of just the agents in the ACKSSuT group was associated with infection.

To assess more definitively whether the exposures identified as risk factors were significantly associated with developing infection with an MDR strain, compared with infection with a pansensitive strain, we compared these 2 groups of patients in the final analysis. Because having an interviewed matched control was not a requisite for the analysis, the additional 36 unmatched patients from among the 202 interviewed patients were available for this final comparison, which made available data for a total of 77 patients infected with MDR strains and 88 infected with pansensitive strains. In univariate analysis, only 2 risk factors were identified as being likely among patients infected with MDR strains than among patients infected with pansensitive strains (table 3), and both remained independently associated with developing infection with an MDR strain according to the results of the multivariate model. In the multivariate model, patients infected with MDR strains were significantly more likely to have been treated with an agent in the ACKSSuT group during the 4 weeks before illness onset (OR, 20.9; 95% CI, 3.6–121.2) and to have eaten home-cooked turkey during the 5 days before illness onset (OR, 4.2; 95% CI, 1.1–16.0) than were patients infected with pansensitive strains. The ACKSSuT antimicrobials received by patients infected with MDR strains during the 4 weeks before illness onset were amoxicillin (by 13 patients) and penicillin (by 2). When we restricted the 77 patients infected with MDR strains to the subset of 51 infected with DT104 (R type ACSSuT), these patients also were more likely to have been treated with agents in the ACKSSuT group than were patients infected with pansensitive strains (OR, 35.3; 95% CI, 5.2–240.1).

We calculated the attributable fraction for each of the identified risk factors in the 2 final models. In the model that compared patients who had MDR *S.* Typhimurium infections with well-matched control subjects, 17% (95% CI, 4%–49%) of the infections with MDR strains were attributed to prior ACKSSuT antimicrobial agent use, whereas 13% (95% CI, 3%–24%) were attributed to consuming scrambled eggs prepared outside the home during the 5 days before illness onset. However, when we compared the patients infected with MDR strains with patients infected with pansensitive strains, 20% (95% CI, 9%–31%) of the infections with MDR strains were attributed to the prior use of ACKSSuT antimicrobial agents and 13% (95% CI, 2%–23%) were attributed to the consumption of turkey cooked in the home.

DISCUSSION

Each year, an estimated 1.4 million *Salmonella* infections occur in the United States, of which ~30,000 are confirmed by culture and have isolates serotyped at state public health laboratories. Previous surveillance data have demonstrated that one particular strain, MDR *S.* Typhimurium DT104 R type ACSSuT, has rapidly disseminated to cause almost 10% of culture-confirmed

human *Salmonella* infections in the United States [6]; similar patterns are occurring in other countries [8, 20]. Recently, the emergence of MDR *S.* Typhimurium R type AKSSuT has also been described in the United States. In the present study, more than one-third of the *S.* Typhimurium infections and, thus, 10% of all *Salmonella* infections occurring in these sites, were identified as being due to MDR strains (predominantly R types ACSSuT and AKSSuT).

We consistently identified one risk factor for development of an MDR *S.* Typhimurium infection: treatment during the 4 weeks before illness onset with antimicrobial agents to which the infecting strain of *S.* Typhimurium was resistant. In particular, prior treatment with agents in the ACKSSuT group was a risk factor for developing infection with an MDR strain if patients infected with pansensitive strains of *S.* Typhimurium, rather than the matched healthy control subjects, were used for comparison. In each instance, case patients infected with MDR strains who received agents in the ACKSSuT group (predominantly β-lactams, such as penicillin and ampicillin) before illness onset were infected with a *Salmonella* isolate that was resistant to that agent. When translated into attributable fractions, having been treated with an antimicrobial agent to which the MDR isolate was resistant accounted for 17% of infections with an MDR strain, if healthy control subjects were used as the baseline population, and accounted for 20% of such infections, if patients infected with pansensitive strains were used as the baseline population.

This phenomenon—exposure to antimicrobial agents that leads to infection with strains resistant to those agents—has also been documented in other recent studies of resistant bacterial organisms [21–24]. On the basis of the results of our study, a biologically plausible explanation is that persons are exposed to low levels of MDR *S.* Typhimurium, likely through the consumption of food products contaminated with resistant organisms, which then establish transient, asymptomatic infections. If the administration of antimicrobial agents to which the MDR *S.* Typhimurium isolate is resistant occurs for any reason during this period of transient infection or at the time of the ingestion of MDR *S.* Typhimurium, the number of susceptible enteric commensal organisms will be reduced. This then permits the proliferation of the MDR *S.* Typhimurium strain resistant to that agent, which results in progression of the infection to a clinically apparent illness. This mechanism does not involve de novo resistance after the exposure of organisms to therapeutic antimicrobial agents in the gastrointestinal tract. Outbreak investigations in which this phenomenon has been evident have demonstrated that patients are infected with organisms that are already resistant. Furthermore, prior antimicrobial agent use does not increase patients' risk for infection with drug-susceptible strains of *Salmonella* to the same extent as it increases the risk for infection MDR *S.* Typhimurium. Our results show that patients' prior use of antimicrobial agents is not a risk factor for development of infection with less-resistant or pansensitive strains, compared with the risk for healthy control subjects. However, when we compared patients infected with an MDR strain with patients infected with a pansensitive strain, we found that prior antimicrobial agent use was a risk factor for infection with an MDR strain.

S. Typhimurium, unlike many other serotypes of *Salmonella,* has caused clinical illness in a wide variety of hosts. The contribution of antimicrobial use in food-animal production to the emergence of antimicrobial resistance in the food-animal population has been extensively discussed [9, 10, 25, 26]. The administration of antimicrobial agents to food-producing animals has created selective pressure for the antimicrobial-resistant strains [27, 28], which has contributed to the dissemination of drug-resistant strains of *Salmonella.* Many reports of clinical illness caused by MDR strains of *S.* Typhimurium among animals have involved cattle [29–31], and sporadic cases and outbreaks of infection with MDR *S.* Typhimurium DT104 (R type ACSSuT) have predominantly been associated with cattle products, such as beef and dairy products [13, 14, 32, 33]. We did not identify any cattle products to be risk factors for infection in our multivariate analysis. Rather, our analyses implicated food-consumption practices associated with poultry—ingestion of home-cooked turkey and various preparations of eggs cooked outside the home. Infections with *S.* Typhimurium and, to a lesser extent, MDR *S.* Typhimurium DT104 (R type ACSSuT) have been associated with poultry and eggs [34–40]. Our results suggest that the role of eggs and poultry in infection with MDR *S.* Typhimurium, specifically in infections with MDR *S.* Typhimurium DT104 (R type ACSSuT), needs to be more fully investigated.

Our study demonstrates that the severity of clinical illness is similar for both patients infected with MDR strains of *S.* Typhimurium and those infected with pansensitive strains. This finding has also been reported in other studies of MDR *S.* Typhimurium, including MDR DT104 R type ACSSuT [41–43], which suggests that these particular organisms may have no greater virulence than other *S.* Typhimurium strains. However, our study did not include persons who did not have diarrhea and, therefore, excluded some persons with severe invasive infections; this exclusion is reflected in the higher proportion of invasive isolates (9%) among patients not enrolled in the study than among patients who were enrolled (3%). Further studies are needed to evaluate the association between infection with an MDR strain and the severity of clinical illness.

Our results also demonstrate the rare but identified resistance to 2 groups of antimicrobial agents that are commonly used to treat persons with serious *Salmonella* infections—the fluor-

oquinolones, for infections in adults, and the extended-spectrum cephalosporins, in children. Although no isolate was resistant to ciprofloxacin, 1% of the MDR *S.* Typhimurium isolates in our study were resistant to the quinolone nalidixic acid, resistance to which correlates with decreased susceptibility to fluoroquinolones. Two isolates (1%) were resistant to ceftriaxone, an extended-spectrum cephalosporin. Treatment failures can be anticipated if resistance to these clinically important antimicrobial agents continues to emerge. Although antimicrobial treatment for uncomplicated salmonellosis is not generally indicated, our results also demonstrate that the treatment of persons who have salmonellosis with antimicrobial agents remains common.

FoodNet is a population-based study. Identifying all culture-confirmed cases within the surveillance areas allows for more accurate estimates of disease incidence. Because control subjects were also selected from the same population, selection bias is limited. Not all identified patients with a culture-confirmed *S.* Typhimurium infection were included in the study, and demographic differences exist between the group of patients included in the case study and those not matched to healthy control subjects, so the risks associated with exposures that may be common to young, elderly, or minority racial/ethnic populations may be underestimated in our study. Recall bias is another possible limitation, because ill persons are more likely to recall specific food exposures than are control subjects. Treatment with antimicrobial agents, however, is likely to be less susceptible to this bias. Recall bias is also not likely to occur in comparisons of patients who are infected with isolates of varying antimicrobial sensitivity. Although any analysis of an array of subgroups can raise concerns about multiple comparisons, the consistent identification of antecedent antimicrobial agent use as a risk factor for infection throughout the analyses suggests that this does not affect our findings. Finally, our study was conducted in only 5 FoodNet sites; because the rates of multidrug resistance and the proportion of DT104 isolates among the *S.* Typhimurium isolates varied by site, the results may not be representative of rates throughout the United States.

To contain antimicrobial resistance, efforts must be made to reduce both the selective pressure created by uses of antimicrobial agents and the transmission of resistant strains. Although guidelines have been established regarding the appropriate use of antimicrobial agents in humans and food animals, clear successes in implementing these guidelines have been few. Continuing efforts are needed to reduce the overuse and misuse of antimicrobial agents in humans and food animals [44, 45]. These efforts will decrease the selective pressure for and resultant emergence of these MDR strains.

FOODNET WORKING GROUP MEMBERS

CDC: Frederick Angulo, Timothy Barrett, Nancy Bean, Thomas Boyce, Laura Conn, Mary Evans, Cindy Friedman, Kate Glynn, Patricia Griffin, John Hatmaker, Debra Helfrick, Thomas Hennessy, Mike Hoekstra, Lori Hutwagner, Kathleen Maloney, Paul Mead, Robert Pinner, Sudha Reddy, Laurence Slutsker, Bala Swaminathan, David Swerdlow, Robert Tauxe, Drew Voetsch, and Samantha Yang Rowe. California: Sharon Abbott, Felicia Chi, Pam Daily, Maryanne David, Mary Ann Davis, Lisa Gelling, Nandeeni Mukerjee, Joelle Nadle, Judy Rees, Kevin Reilly, Art Reingold, Gretchen Rothrock, Michael Samuel, Sue Shallow, Duc Vugia, Stephen Waterman, and Ben Werner. Connecticut: Matthew Cartter, Terry Rabatsky-Ehr, James Hadler, Robert Howard, Gazala Khan, Ruthanne Marcus, Donald Mayo, Pat Mshar, and Robin Ryder. Georgia: Molly Bardsley, Wendy Baughman, Paul Blake, Shama Desai, Monica Farley, Jane Koehler, Mina Pattani, Susan Ray, Matthew Sattah, Suzanne Segler, Kathleen Toomey, and Sabrina Whitfield. Maryland: Bernadette Albanese, Lillian Billman, Amy Carnahan, Michael Carter, Marcia Crisco, Diane Dwyer, Lora Gay, Lee Harrision, Kelly Henning, Yvonne Hibbert, Jackie Hunter, Judith Johnson, Melissa Kent, J. Glenn Morris, Jr., Peggy Pass, Jeffery Roche, and Christine St. Ours. Minnesota: Jeff Bender, John Besser, Valerie Deneen, Craig Hedberg, Julie Hogan, Heidi Kassenborg, Michael Osterholm, and Julie Wicklund. New York: Hwa-Gan Chang, Karim Hechemy, Julie Keihlbauch, Dale Morse, Brian Sauders, Cathy Stone, and Shelley Zansky. Oregon: Maureen Cassidy, Paul Cieslak, David Fleming, Bill Keene, Stephen Ladd-Wilson, Steve Mauvais, Teresa McGivern, Beletshachew Shiferaw, Bob Sokolow, Regina Stanton, and John Townes. US Department of Agriculture, Food Safety Inspection Service: Art Baker, Ruth Etzel, Jim Hollingsworth, Peggy Nunnery, Phyllis Sparling, and Kaye Wachsmuth. US Food and Drug Administration, Center for Food Safety and Applied Nutrition: Sean Alterkruse, Ken Falci, Bing Garthright, and Janice Oliver.

Acknowledgments

We thank the FoodNet and public health laboratory staff for their significant contributions to the study and Malinda Kennedy, of the Foodborne and Diarrheal Diseases Branch, Centers for Disease Control and Prevention, for her assistance with data management.

References

1. Mead PS, Slutsker L, Dietz V, et al. Food-related illness and death in the United States. Emerg Infect Dis **1999**; 5:607–25.
2. Frenzen PD, Riggs TL, Buzby JC, et al. *Salmonella* cost estimates updated using FoodNet data. Food Rev **1999**; 22:10–5.
3. Centers for Disease Control and Prevention. *Salmonella* surveillance:

annual tabulation summary 1999. Atlanta: US Department of Health and Human Services, **2000**.
4. Lee LA, Puhr ND, Maloney EK, Bean NH, Tauxe RV. Increase in antimicrobial-resistant *Salmonella* infections in the United States, 1989–1990. J Infect Dis **1994**; 170:128–34.
5. MacDonald KL, Cohen ML, Hargrett-Bean NT, et al. Changes in antimicrobial resistance of *Salmonella* isolated from humans in the United States. JAMA **1987**; 258:1496–9.
6. Glynn MK, Bopp C, DeWitt W, et al. Emergence of multidrug-resistant *Salmonella enterica* serotype Typhimurium DT104 infections in the United States. N Engl J Med **1998**; 338:1333–7.
7. Centers for Disease Control and Prevention. National antimicrobial resistance monitoring system: enteric bacteria, 1999 annual report. Atlanta: US Department of Health and Human Services, **2000**.
8. Seyfarth AM, Wegener HC, Frimodt-Moller N. Antimicrobial resistance in *Salmonella enterica* subsp. *enterica* serovar Typhimurium from humans and production animals. J Antimicrob Chemother **1997**; 40: 67–75.
9. Angulo FJ, Johnson KR, Tauxe RV, Cohen ML. Significance and sources of antimicrobial-resistant nontyphoidal *Salmonella* infections in the United States. Microb Drug Resist **2000**; 6:77–83.
10. O'Brien TF, Hopkins JD, Gilleece ES, et al. Molecular epidemiology of antibiotic resistance in *Salmonella* from animals and human beings in the United States. N Engl J Med **1982**; 307:1–6.
11. Holmberg SD, Wells JG, Cohen ML. Animal-to-man transmission of antimicrobial-resistant *Salmonella:* investigations of U.S. outbreaks, 1971–1983. Science **1984**; 225:833–5.
12. Molbak K, Baggesen DL, Aarestrup FM, et al. An outbreak of multidrug-resistant, quinolone-resistant *Salmonella enterica* serotype Typhimurium DT104. N Engl J Med **1999**; 341:1420–5.
13. Villar RG, Macek MD, Simons S, et al. Investigation of multidrug-resistant *Salmonella* serotype Typhimurium DT104 infections linked to raw-milk cheese in Washington State. JAMA **1999**; 281:1811–6.
14. Cody SH, Abbott SL, Marfin AA, et al. Two outbreaks of multidrug-resistant *Salmonella* serotype Typhimurium DT104 infections linked to raw-milk cheese in northern California. JAMA **1999**; 281:1805–10.
15. Centers for Disease Control and Prevention. 1996 Final FoodNet surveillance report. Atlanta: US Department of Health and Human Services, **1998**.
16. NCCLS. Performance standards of antimicrobial disk susceptibility tests. Publication M100-S6. Wayne, PA: NCCLS, **1995**.
17. Anderson ES, Ward LR, deSaxe MJ, deSa JD. Bacteriophage-typing designations of *Salmonella typhimurium.* J Hyg (Lond) **1977**; 78: 297–300.
18. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol **1985**; 122:904–14.
19. Kahn MJ, O'Fallon WM, Sicks JD. General population attributable risk estimation. Technical report 54. Rochester, MN: Mayo Clinic, **2000**.
20. Threlfall EJ, Ward LR, Skinner JA, Rowe B. Increase in multiple antibiotic resistance in nontyphoidal salmonellas from humans in England and Wales: a comparison of data for 1994 and 1996. Microb Drug Resist **1997**; 3:263–6.
21. Riley LW, Cohen ML, Seals JE, et al. Importance of host factors in human salmonellosis caused by multiresistant strains of *Salmonella.* J Infect Dis **1984**; 149:878–83.
22. Delarocque-Astagneu E, Boulliant C, Vaillant V, et al. Risk factors for the occurrence of sporadic *Salmonella enterica* serotype Typhimurium in children in France: a national case-control study. Clin Infect Dis **2000**; 31:488–92.
23. Arason VA, Kristinsson KG, Sigurdsson JA, et al. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. BMJ **1996**; 313:387–91.
24. Allen UD, MacDonald N, Fuite L, Chan F, Stephens S. Risk factors for resistance to "first-line" antimicrobials among urinary tract isolates of *Escherichia coli* in children. CMAJ **1999**; 160:1436–40.
25. Witte W. Medical consequences of antibiotic use in agriculture. Science **1998**; 279:996–7.
26. Cohen ML, Tauxe RV. Drug-resistant *Salmonella* in the United States: an epidemiologic perspective. Science **1986**; 234:964–9.
27. Levy SB. Multidrug resistance—a sign of the times. N Engl J Med **1998**; 338:1376–8.
28. Wegener HC, Aarestrup FM, Jensen LB, Hammerum AM, Bager F. Use of antimicrobial growth promoters in food animals and *Enterococcus faecium* resistance to therapeutic antimicrobial drugs in Europe. Emerg Infect Dis **1999**; 5:329–35.
29. Threlfall EJ, Frost JA, Ward LR, Rowe B. Epidemic in cattle and humans of *Salmonella typhimurium* DT104 with chromosomally integrated multiple drug resistance. Vet Rec **1994**; 134:577.
30. Evans S, Davies R. Case control study of multiple-resistant *Salmonella typhimurium* DT104 infection of cattle in Great Britain. Vet Rec **1996**; 139:557–8.
31. Low JC, Angus M, Hopkins G, Munro D, Rankin SC. Antimicrobial resistance of *Salmonella enterica* Typhimurium DT104 isolates and investigation of strains with transferable apramycin resistance. Epidemiol Infect **1997**; 118:97–103.
32. Davies A, O'Neill P, Towers L, Cooke M. An outbreak of *Salmonella typhimurium* DT104 food poisoning associated with eating beef. Commun Dis Rep CDR Rev **1996**; 6:R159–62.
33. Anonymous. Defective pasteurisation linked to outbreak of *Salmonella* Typhimurium definitive phage type 104 infection in Lancashire. Commun Dis Rep CDR Wkly **1998**; 8:335, 338.
34. Threlfall EJ, Brown D, Rowe B, Ward LR. Multiple drug-resistant strains of *Salmonella* Typhimurium in poultry. Vet Rec **1989**; 124:538.
35. Brown DJ, Threlfall EJ, Rowe B. Instability of multiple drug resistance plasmids in *Salmonella* Typhimurium isolated from poultry. Epidemiol Infect **1991**; 106:247–57.
36. Davies RH, Teale CJ, Wray C, et al. Nalidixic acid resistance in salmonellae isolated from turkeys and other livestock in Great Britain. Vet Rec **1999**; 144:320–2.
37. Rajashekara G, Haverly E, Halvorson DA, et al. Multidrug-resistant *Salmonella* Typhimurium DT104 in poultry. J Food Prot **2000**; 63: 155–61.
38. Hedberg CW, David MJ, White KE, MacDonald KL, Osterholm MT. Role of egg consumption in sporadic *Salmonella* Enteritidis and *Salmonella* Typhimurium infections in Minnesota. J Infect Dis **1993**; 167: 107–11.
39. Grein T, O'Flanagan D, McCarthy T, Bauer D. An outbreak of multidrug-resistant *Salmonella* Typhimurium food poisoning at a wedding reception. Ir Med J **1999**; 92:238–41.
40. Williams A, Davies AC, Wilson J, et al. Contamination of the contents of intact eggs by *Salmonella* Typhimurium DT104. Vet Rec **1998**; 143: 562–3.
41. Threlfall EJ, Ward LR, Rowe B. Multiresistant *Salmonella* Typhimurium DT 104 and *Salmonella* bacteraemia. Lancet **1998**; 352:287–8.
42. Carlson SA, Willson RM, Crane AJ, Ferris KE. Evaluation of invasion-conferring genotypes and antibiotic-induced hyperinvasive phenotypes in multiple antibiotic resistant *Salmonella* Typhimurium DT104. Microb Pathog **2000**; 28:373–8.
43. Carlson SA, Browning M, Ferris KE, Jones BD. Identification of diminished tissue culture invasiveness among multiple antibiotic resistant *Salmonella* Typhimurium DT104. Microb Pathog **2000**; 28:37–44.
44. Belongia EA, Schwartz B. Strategies for promoting judicious use of antibiotics by doctors and patients. BMJ **1998**; 317:668–71.
45. Levin BR, Antia R, Berliner E, et al. Resistance to antimicrobial chemotherapy: a prescription for research and action. Am J Med Sci **1998**; 315:87–94.